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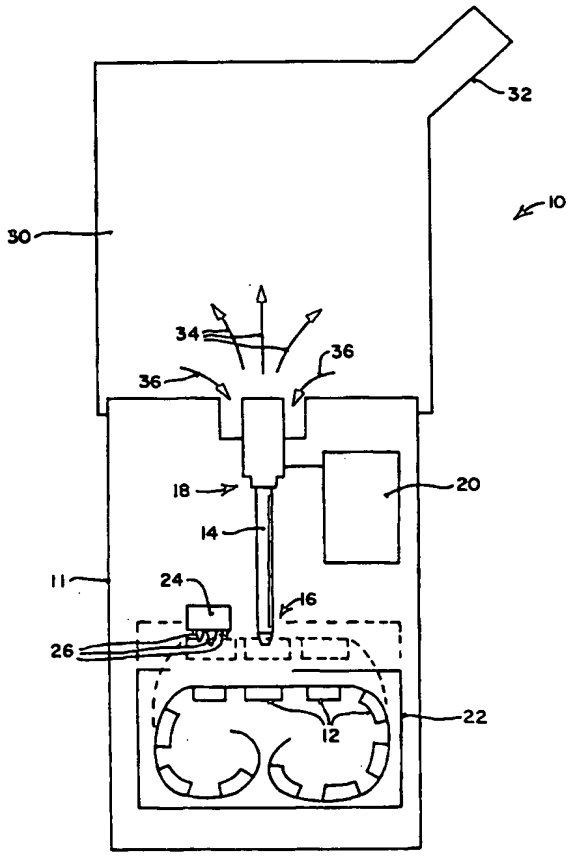
(54) Title: APPARATUS AND METHODS FOR DISPERSING DRY POWDER MEDICAMENTS

(57) Abstract

A method for aerosolizing a powdered medicament comprises coupling a powder inlet end of a feed tube (14) with a penetration in a receptacle (12) containing the powder. Powder is drawn upward through the tube and dispersed in a high pressure gas stream flowing past a portion of the feed tube. Apparatus comprises the feed tube mounted within a base enclosure proximate a holder for one or more receptacles, which may be formed in a continuous web placed in a cartridge (22). A separate piercing mechanism (26) may be provided.



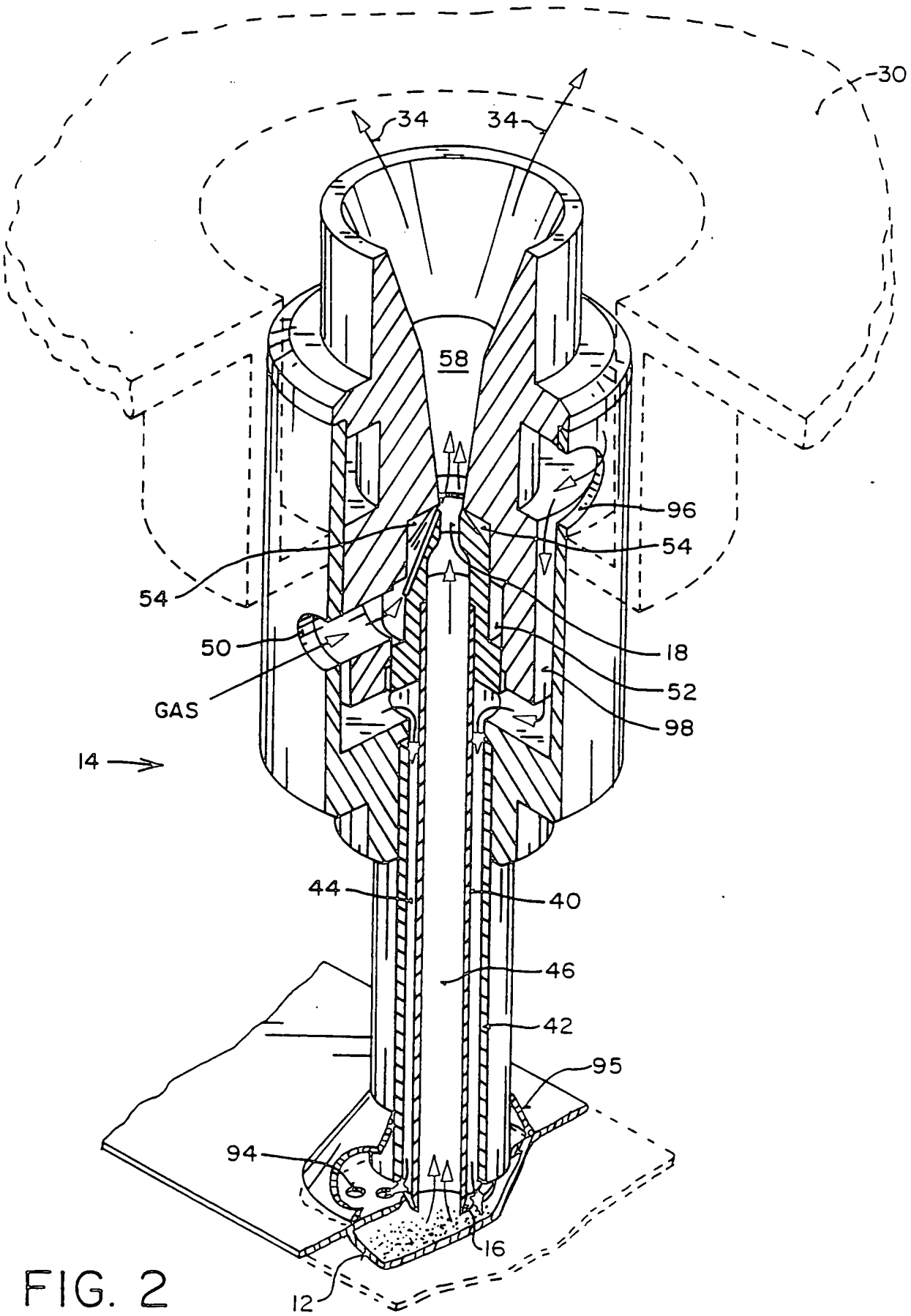


FIG. 2

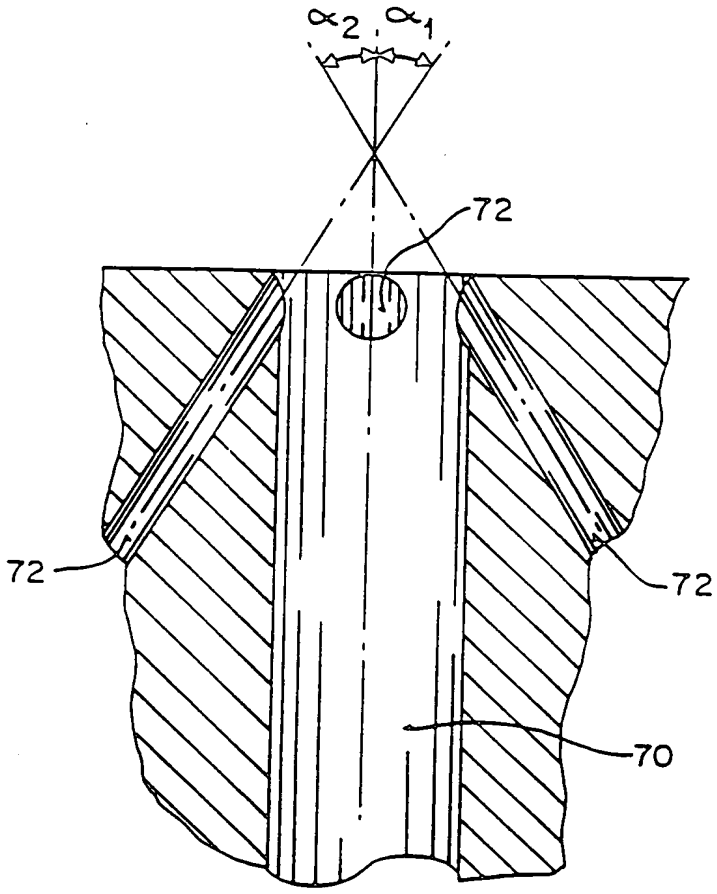


FIG. 5

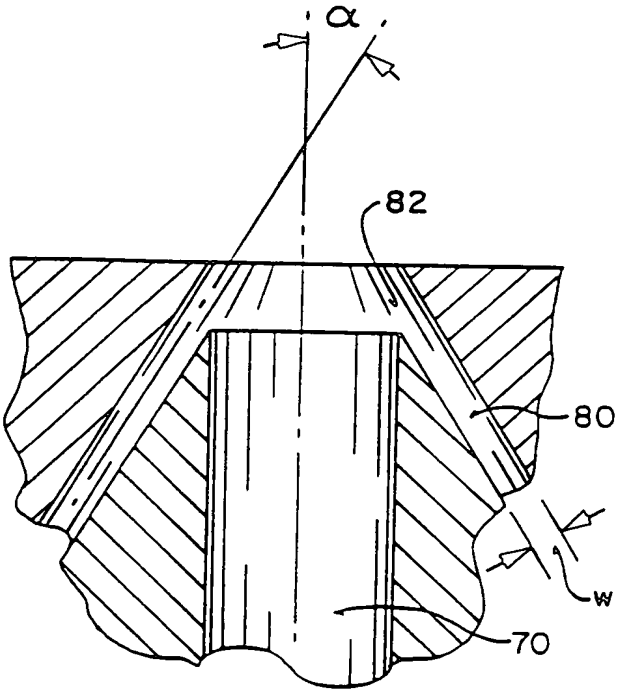


FIG. 6

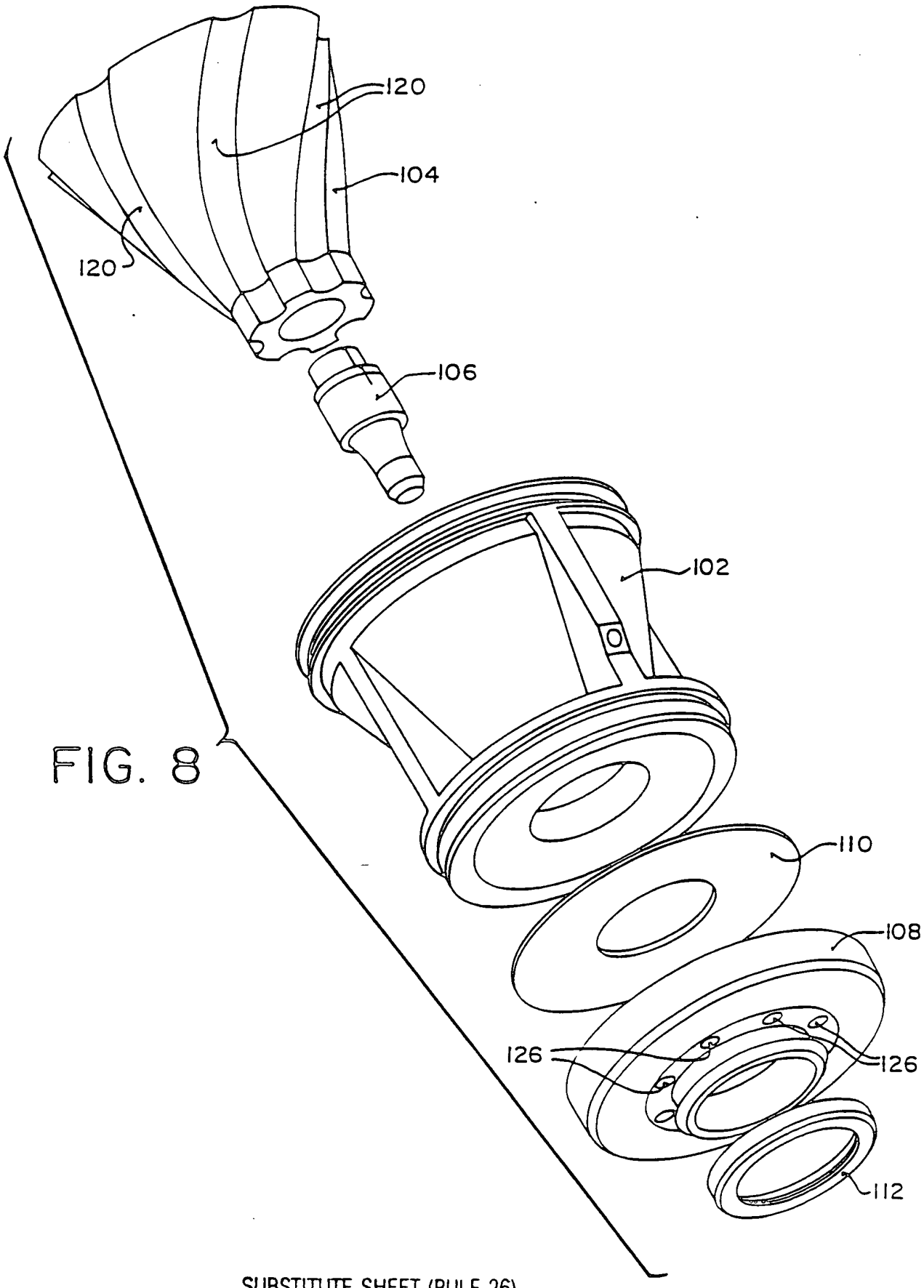


FIG. 8

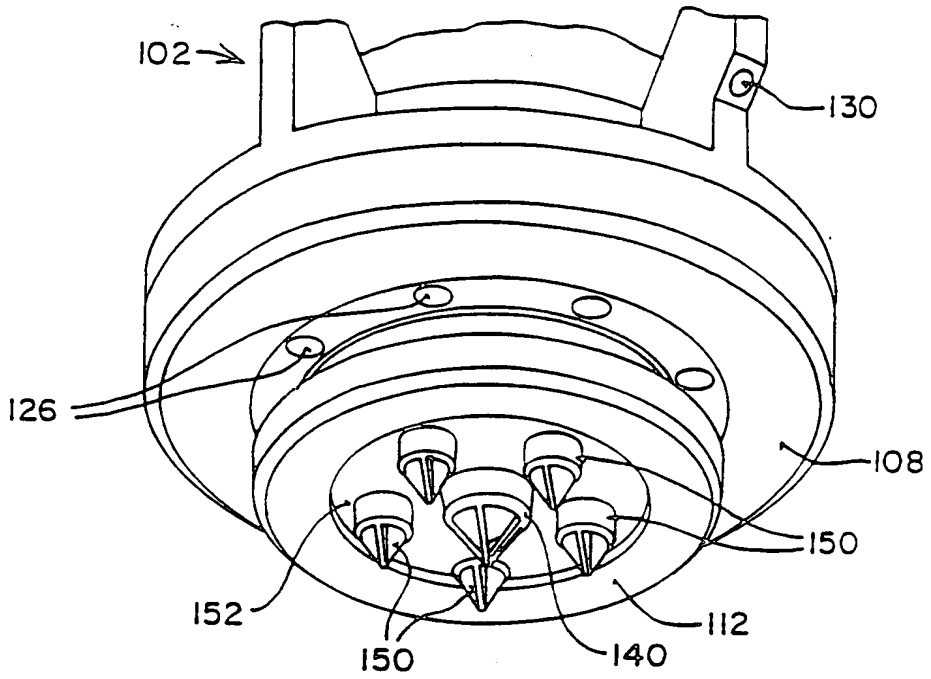


FIG. 10

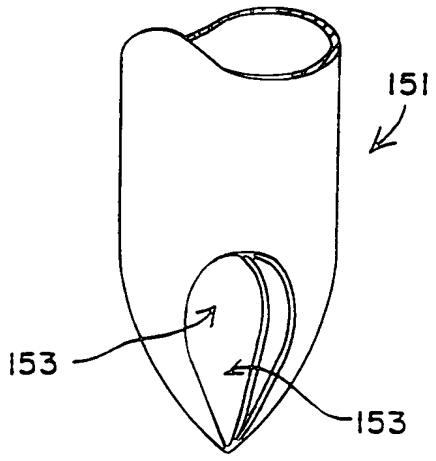


FIG. 11B

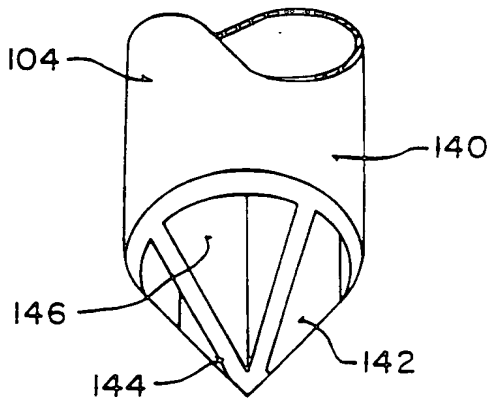


FIG. 11A

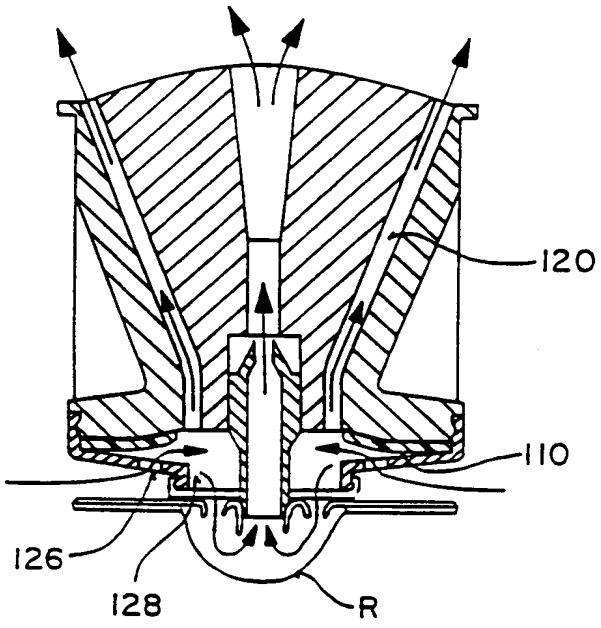


FIG. 12C

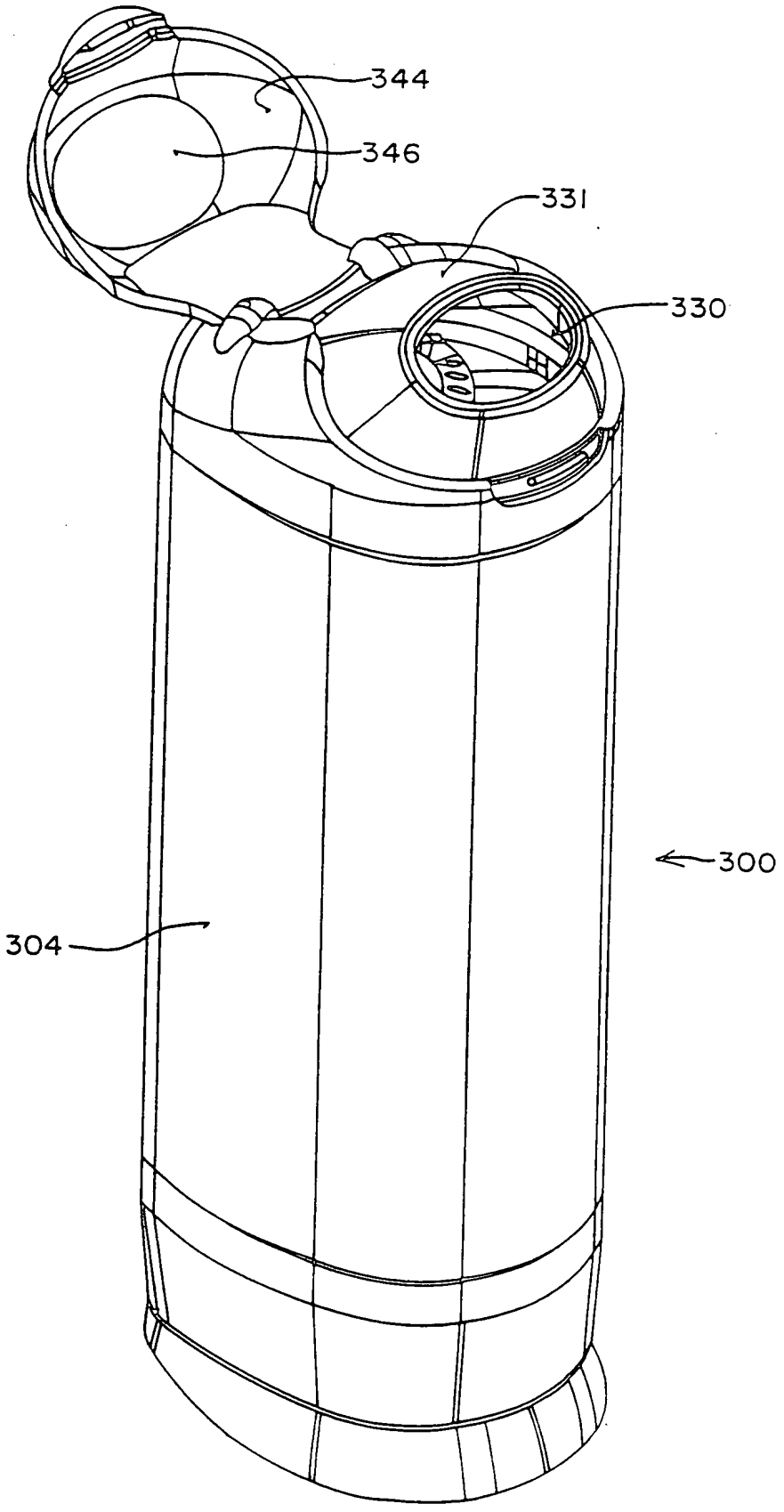


FIG. 14

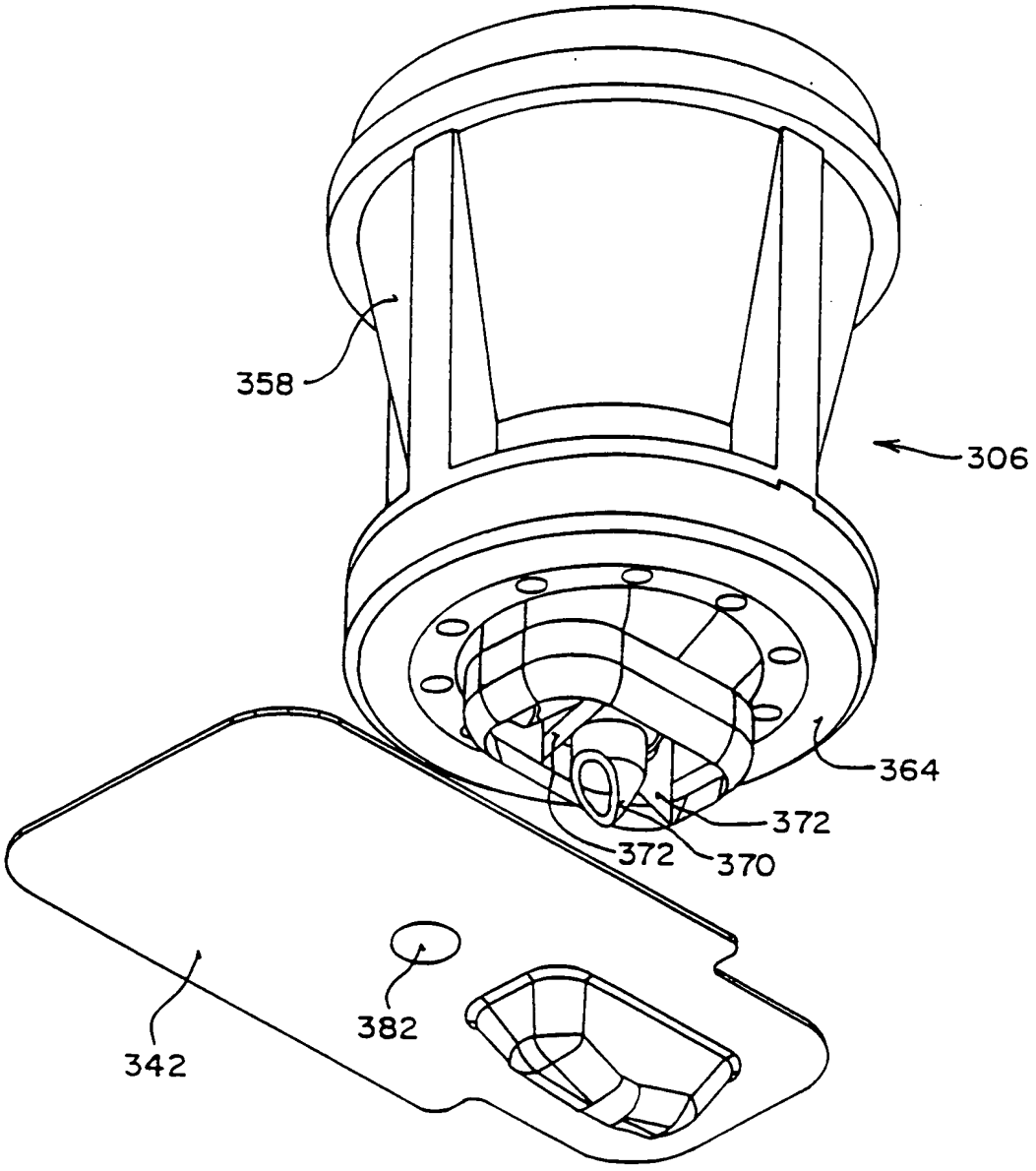


FIG. 16

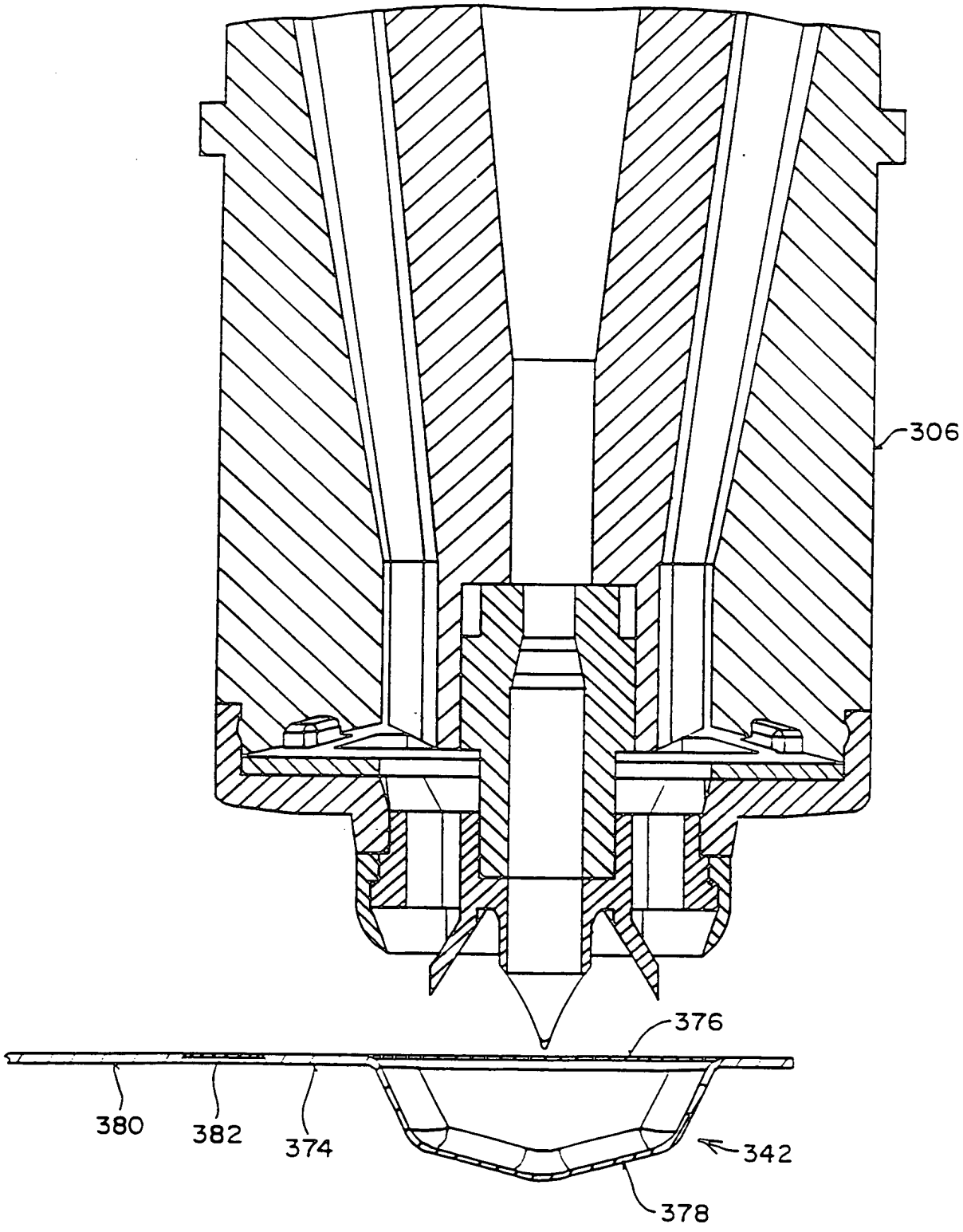


FIG. 18

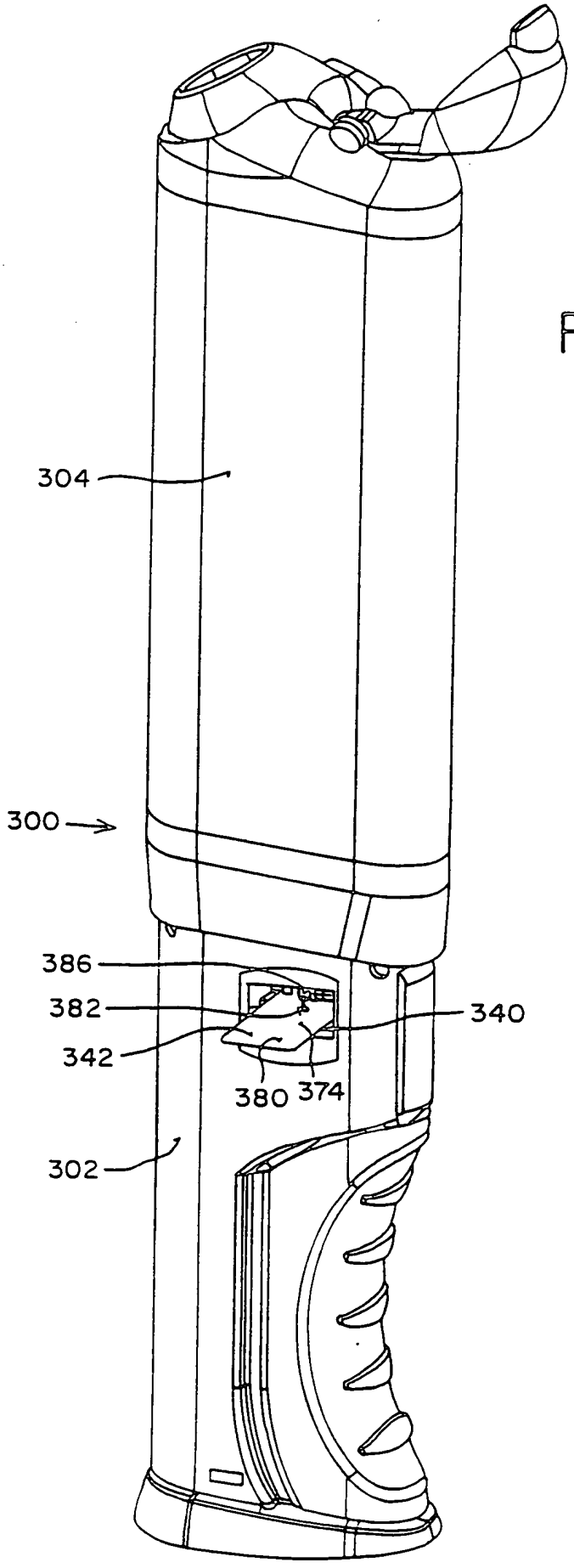


FIG. 20

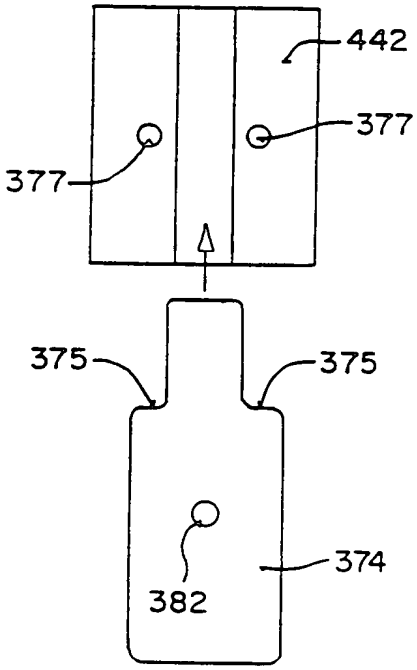


FIG. 20A

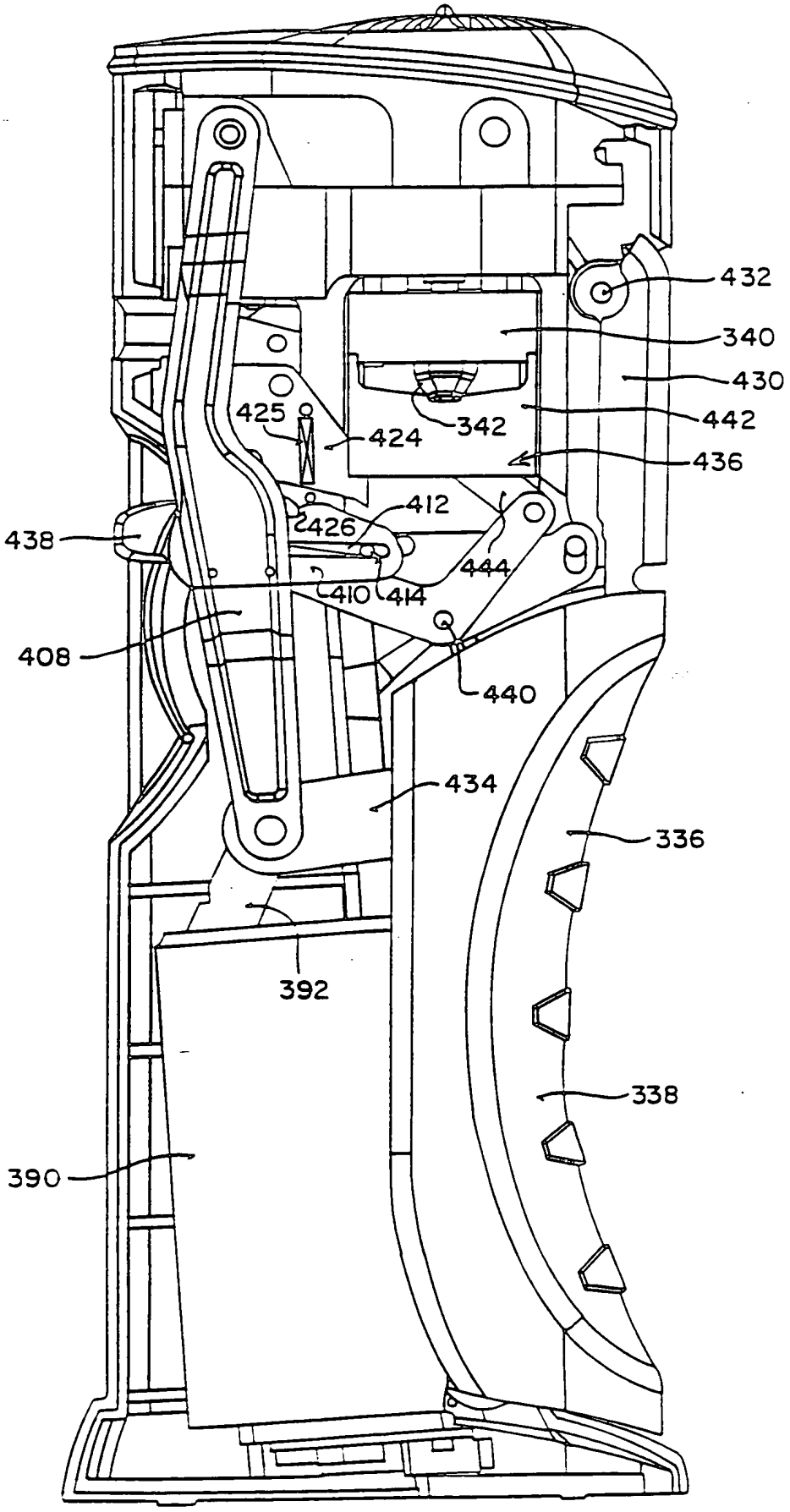

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FIG. 22

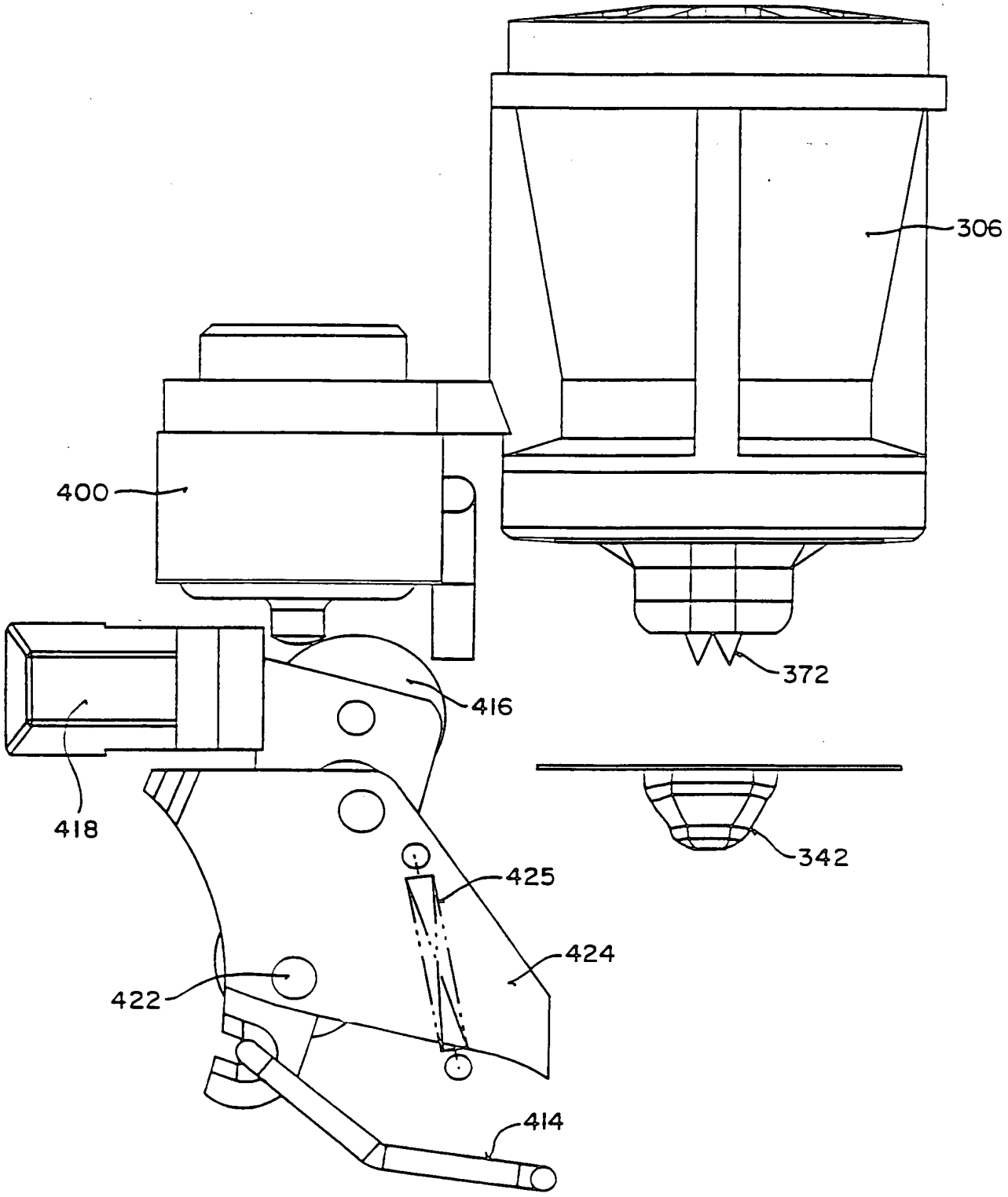

FIG. 24

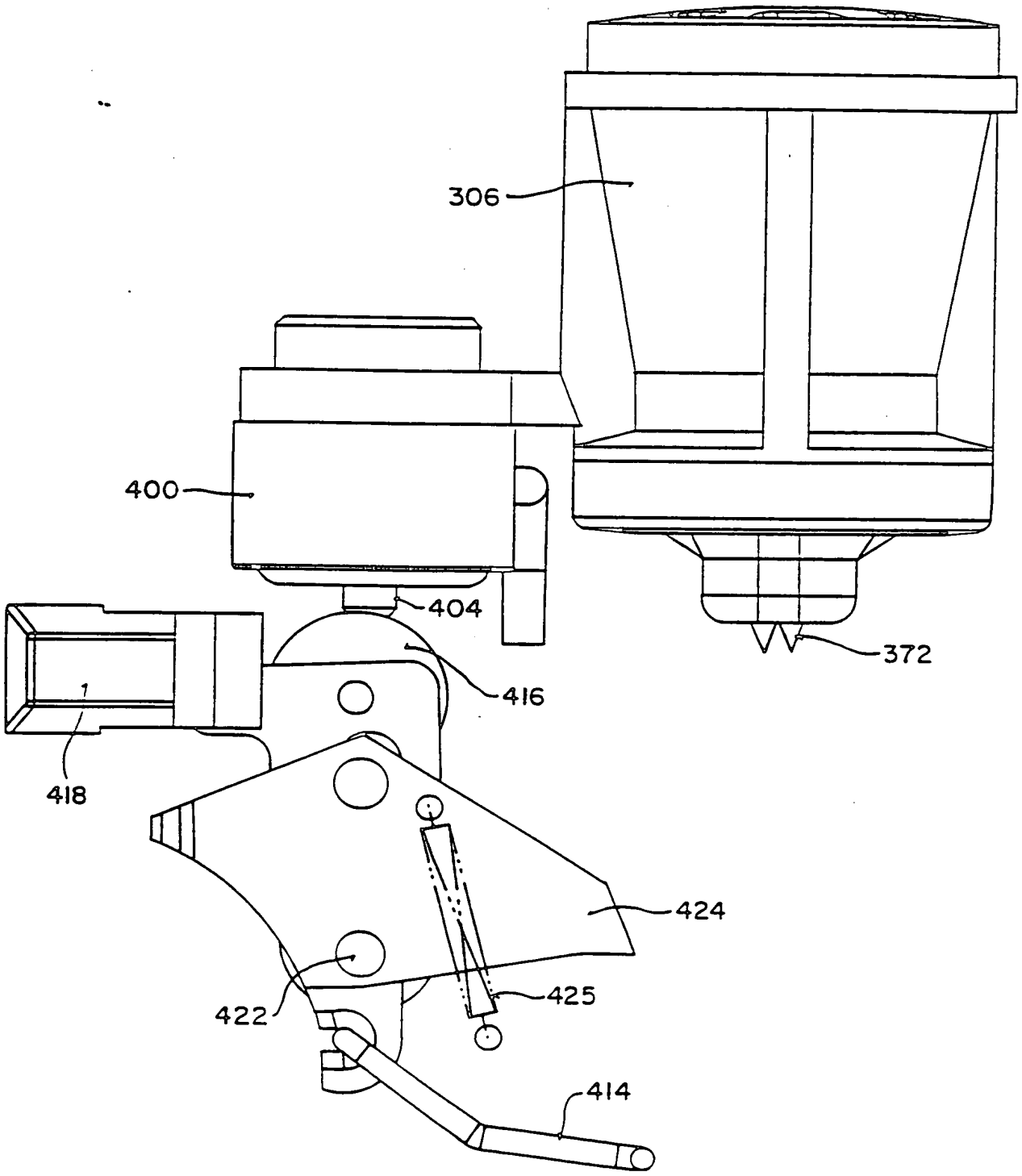

FIG. 26

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/11655

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 5207217 (COCOZZA ET AL) 08 May 1993. See entire document.	1-11
A	US, A, 5186166 (RIGGS ET AL) 16 February 1993. See entire document.	1-11

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/11655

Box I Observations where certain claims were f und unsearchable (Continuation f item 1 f first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-11

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

APPARATUS AND METHODS FOR DISPERSING DRY POWDER MEDICAMENTS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates generally to methods and apparatus for the pulmonary delivery of drugs. More particularly, the present invention relates to a method and apparatus for dispersing dry powder medicaments for inhalation by a patient.

Effective delivery to a patient is a critical aspect of any successful drug therapy. Various routes of delivery exist, and each has its own advantages and disadvantages. Oral drug delivery of pills, capsules, elixirs, and the like, is perhaps the most convenient method, but many drugs are degraded in the digestive tract before they can be absorbed. Such degradation is a particular problem with modern protein drugs which are rapidly degraded by proteolytic enzymes in the digestive tract. Subcutaneous injection is frequently an effective route for systemic drug delivery, including the delivery of proteins, but enjoys a low patient acceptance. Since injection of drugs, such as insulin, one or more times a day can frequently be a source of poor patient compliance, a variety of alternative routes of administration have also been developed, including transdermal, intranasal, intrarectal, intravaginal, and pulmonary delivery.

Of particular interest to the present invention, pulmonary drug delivery relies on inhalation of a drug dispersion or aerosol by the patient so that active drug

problematic in a number of other respects. The particles being delivered are very fine, usually being sized in the range from 1μm to 5μm, making powder handling and dispersion difficult. The problems are exacerbated by the relatively small volumes of pressurized gas, typically 2 ml to 25 ml at 20 to 150 psig, which are available in such devices. In particular, Venturi tube dispersion devices are unsuitable for difficult-to-disperse powders when only small volumes of pressurized gas are available. Moreover, Venturi tube dispersion devices have very small powder inlet orifices which are easily plugged by the powders used for pulmonary delivery. Another requirement for hand-held and other powder delivery devices is high dosage concentration. It is important that the concentration of drug in the bolus of gas be relatively high to reduce the number of breaths and/or volume of each breath required to achieve a total dosage. The ability to achieve both adequate dispersion and small dispersed volumes is a significant technical challenge.

It would therefore be desirable to provide methods and systems for the dispersion of dry powder protein, polypeptide, and other drugs which meet some or all of the above objectives.

2. Description of the Background Art

Dry powder dispersion devices for medicaments are described in a number of patent documents. U.S. Patent 3,921,637 describes a manual pump with needles for piercing through a single capsule of powdered medicine. The use of multiple receptacle disks or strips of medication is described in EP 467172 (where a reciprocatable piercing mechanism is used to piercing mechanism through opposed surfaces of a blister pack); WO91/02558; WO93/09832; WO94/08522; US Patent Nos. 4,627,432; 4,811,731; 5,035,237; 5,048,514; 4,446,862; and 3,425,600. Other patents which show puncturing of single medication capsules include 4,338,931; 3,991,761; 4,249,526; 4,069,819; 4,995,385; 4,889,114; and 4,884,565; and EP 469814. WO90/07351 describes a hand-held pump device with a loose powder reservoir.

U.S. Patent No. 3,994,421, describes a hand-held powder disperser having a collapsible deceleration chamber.

Pulmonary drug delivery is described in Byron and Patton (1994) J. Aerosol Med. 7:49-75.

SUMMARY OF THE INVENTION

The present invention provides methods and apparatus for efficient pulmonary delivery of accurate, precise, and repeatable dosages of powdered medicaments. The present invention will be particularly useful for the delivery of costly biopharmaceuticals such as protein, polypeptide and polynucleic acid drugs, but will also be useful for the systemic or localized delivery of any powdered medicament through the lungs. The delivery system and method produce substantially complete dispersion of the medicament powder with the break-up of any agglomerates of the powder which may have formed prior to delivery. The method and apparatus will find particular use in the dispersion of finely powdered medicaments from unit dosage receptacles, such as blister packs or cartridges, where the present invention is able to fluidize and extract substantially the entire amount of powder (usually at least 70% by weight, more usually at least 80%, and preferably at least 90%) within the receptacle, thus minimizing waste and enhancing the accuracy and precision of the dosage. The methods and approaches, however, will also find use with the dispersion and delivery of preselected metered amounts (boluses) of powdered medicaments from receptacles containing multiple dosage units, i.e. "bulk" powders contained in a single receptacle.

The methods and apparatus of the present invention are particularly suitable for the delivery of powders formed from discrete particles in the size range from 1μm to 5μm. Such powders, when properly dispersed in an aerosol, are optimum for delivery into the alveolar regions of the lung. However, they are particularly difficult to handle, and frequently become highly agglomerated during processing, packaging, and handling. Heretofore, handling characteristics of such powders have often been enhanced by combining the fine

of fluidization air to enter the receptacle, fluidize the powder, and sweep the receptacle of the fluidized powder to help assure that substantially all powder (preferably at least 70%, more preferably at least 80%, and still more preferably at least 90%) is removed into the flowing air stream. The high pressure gas stream will be generated by abruptly releasing a charge of pressurized gas through a flow path which intersects with the outlet end of the feed tube at an angle selected to both (1) induce sufficient fluidization air flow through the feed tube to fluidize and transport powder in the receptacle and (2) break up powder agglomerates which remain as the powder exits from the outlet end of the feed tube. The gas pressure prior to release will usually be at least about 15 psig (to achieve sonic velocity), preferably being at least 20 psig, and more preferably being in the range from 20 psig to 150 psig, and usually being in the range from 40 psig to 80 psig. The expanded volume of released gas (measured at standard temperature and pressure (STP) of 14.7 psig and 20°C) will thus usually be in the range from 2 ml to 25 ml, preferably being from 4 ml to 15 ml. Release of the high pressure gas can be effected by a manual trigger or optionally by sensing negative pressure resulting from the patient's inspiration (i.e., can be breath-activated). As described in detail below, the high pressure gas stream will combine with the fluidization air stream at a volume ratio (measured at STP) in the range from 1:2 to 1:4 (high pressure gas: fluidization air) to produce the aerosol which is subsequently inhaled by the patient, optionally after capture in a plume capture chamber.

The method may further comprise the step of capturing the resulting discrete volume of aerosolized powder in a plume capture chamber prior to subsequent inhalation by the patient. The patient is then able to inhale the entire aerosolized dose from the chamber, concurrently with and/or followed by inhalation of ambient air which sweeps the capture chamber to further assure efficient delivery of the powder with minimum losses. Inhalation of chase air following the initial bolus of medication will drive the medication deep

resulting low pressure region at the outlet end of the feed tube draws fluidization air into the receptacle (preferably from the plume capture chamber which subsequently receives the aerosol, thus minimizing net air introduced from outside the device) to fluidize and extract the powder outward from the receptacle through the tube, and into the high velocity gas stream to form the desired dispersion. Usually, the capture chamber is disposed over and in-line with the outlet end of the feed tube to contain the "plume" of powder aerosol and allow the plume to quiesce prior to inhalation by the patient. The feed tube does not have jets or ejector tubes within the flow path, and the clear, undisrupted flow path reduces any tendency for the feed tube to clog or otherwise lose dispersion efficiency. Using air from the capture chamber as a source of fluidization gas is advantageous since it reduces the total volume of "new" gas introduced to the chamber, making capture of the dispersion gas stream (i.e., the combination of the high pressure gas stream and the fluidization air stream) easier. Such recycling of air from the capture chamber, however, is not an essential feature of the present invention. Fluidization air can also be obtained directly from outside the device.

In a particular aspect of the apparatus of the present invention, the receptacle will be supported in a mechanism for advancing a continuous web (e.g. a strip or disk) which carries a plurality of receptacles past the fluidization location. Usually, the web advance mechanism includes a cartridge or carriage which holds the web and which is reciprocatably mounted relative to the feed tube so that the receptacles may be sequentially advanced while the cartridge and tube are separated, and the tube thereafter introduced into the receptacle by moving the cartridge and tube together. Optionally, the receptacle lid or other single access surface (i.e., a surface on one side of the receptacle) will be pierced immediately prior to introduction of the feed tube, usually using a separate piercing mechanism which pierces the lid as the cartridge is reciprocated relative to the feed tube. Alternatively, the access surface can be

substantially break up agglomerates which are present in the powder.

The aerosolizing apparatus may include two or more separate gas conduits which converge from different, usually opposite (diametrically opposed), sides of the flow path. Alternatively, the high pressure gas conduit may terminate in a single annular aperture which circumscribes the outlet end of the feed tube and which creates a gas flow path which converges on the axial flow path. The latter approach however, will generally be less preferred since it is difficult to manufacture annular apertures in the small size required. The total lumen area (A_1) of the high pressure (dispersion) gas flow conduit(s) will usually be in the range from 0.05 mm^2 to 0.3 mm^2, while the throat of the feed tube immediately upstream of the gas conduit(s) tube will have a lumen area (A_2) in the range from 0.5 mm^2 to 10 mm^2. The area (A_3) and length of the mixing volume immediately downstream from the high velocity gas conduits are preferably in the range from the 0.6 mm^2 to 11 mm^2 and 0.5 mm to 3 mm, respectively. The feed tube upstream of the throat will usually have an area (A_4) in the range from 0.6 mm^2 to 15 mm^2.

The aerosolizing apparatus may further include a diffuser tube extending from the outlet end of the mixing volume and having a lumen which is usually but not necessarily coaxially aligned with the feed tube lumen. The diameter of the diffuser tube lumen will increase in a direction away from the outlet end of the mixing volume, typically diverging at a half angle of 2° to 10° over a length in the range from 0.5 cm to 5 cm, usually having an outlet area which is about four times the inlet (mixing volume) area. The diffuser tube thus causes a reduction in the velocity of the gas stream exhausted from the outlet end of the mixing volume, where velocity is at a maximum, prior to entering the plume capture chamber. The plume continues to slow rapidly as it expands within the chamber and approaches a quiet or quiescent state prior to inhalation.

The present invention further provides a feed tube assembly comprising a casing, a flow-directing member, and a

provided for translating the roller cam from the over-center position to open the valve. In yet a further aspect, the cylinder preferably includes a one-way valve for allowing air to enter the cylinder as the piston is translated to the retracted position.

In one particular aspect, the powdered medicament is held within a receptacle. A feed tube is provided having an inlet end, an outlet end, and a lumen extending therebetween so that the inlet end may be inserted into the receptacle. In this way, compressed gas exiting the release valve may be flowed past the outlet end of the feed tube, with powder from the receptacle being extracted through the tube and dispersed in the flowing compressed gas to form the aerosol. Preferably, a means is provided for piercing at least one hole in an access surface of the receptacle simultaneously with inserting the inlet end of the feed tube into the receptacle. In a preferable aspect, the piercing means comprises a pair of pointed tabs, with the tabs being each disposed at an oblique angle relative to the access surface of the receptacle when the tabs are pierced through the access surface.

In another particular aspect, a means is provided for reciprocally translating the receptacle toward and away from the piercing means. The translating means preferably includes an over-center linkage for locking the receptacle in place upon insertion of the inlet end of the feed tube into the receptacle. In another aspect, a positioning pin is provided for aligning the receptacle in a preferred orientation relative to the piercing means while inserting the inlet end of the feed tube into the receptacle.

In yet another particular aspect, the handle assembly includes four linkages for attaching the handle to the housing. In this manner, the handle may be translated radially outward and radially inward relative to the housing with a generally constant force, and with a more linear motion than with a simple pivot. Further, such linkages reduce the distance that the handle must be translated away from the housing, thereby making easier hand operation of the handle assembly. In another aspect, a means is provided on or in

the body. The elongate ridge engages the housing when the chamber is collapsed to limit the amount of accumulated powder on the chamber that may be scraped from the chamber by the housing. In yet another aspect, the chamber body is asymmetrical in cross-sectional geometry and includes a mouthpiece. A cap is preferably removably held over the mouthpiece to prevent external dust and particulate from entering the chamber and to hold the powdered medicament within the chamber until ready to be inhaled. A seal is preferably provided between the cap and the mouthpiece, with the seal preferably being configured to function as a bleed valve to allow excess gas within the chamber to escape.

The invention further provides a receptacle for holding a powdered medicament, with the receptacle being adapted to be received into a housing of an aerosolizing apparatus. The receptacle includes a receptacle body having a puncturable access surface and a tab extending from the receptacle body. In this manner, the receptacle body may be received into an aperture in the housing with at least a portion of the tab remaining outside the housing. In one aspect, the tab includes a keyed hole adapted to receive an alignment pin in the aerosolizing apparatus. By keying the hole in the tab, the receptacle may be configured so that it may only be used with an apparatus having a mating alignment pin. In this way, the apparatus may be configured to receive only certain receptacles having a particular medicament.

The invention provides an improved method for aerosolizing a powdered medicament. The method is of the type wherein the powder is entrained and suspended in a flowing gas stream and comprises providing a housing having a pressurization cylinder, a piston slidable within the cylinder, a release valve in communication with the cylinder, and a handle for axially translating the piston and for closing the release valve. The handle is initially translated away from the housing to axially translate the piston within the cylinder to a retracted position and to close the release valve. The handle is then translated back toward the housing to translate the piston to a position where it creates a

that at least a portion of the tab remains outside the housing. The receptacle body is raised and simultaneously pierced and the powdered medicament in the receptacle is extracted in a gas stream that can be inhaled. The receptacle is lower, and the tab is then pulled to remove the receptacle from the housing.

In one aspect, the housing has a reciprocatable capture chamber for receiving the powder-bearing gas stream, and the chamber is preferably deployed prior to inserting the receptacle. Deploying of the chamber exposes the aperture, and insertion of the receptacle into the aperture prevents the chamber from retracting until the receptacle is removed.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic illustration of an aerosol dispersion system constructed in accordance with the principles of the present invention.

Fig. 2 is a perspective illustration of a powder feed tube assembly employed in the aerosol dispersion system of Fig. 1, shown in quarter-section with its inlet end proximate a powder receptacle.

Fig. 3 illustrates a preferred powder receptacle lid penetration pattern.

Fig. 4A is a cross-sectional view of a portion of the feed tube assembly illustrated in Fig. 2.

Fig 4B is a cross-sectional view taken along line 4B-4B of Fig. 4A.

Fig. 4C is an alternative cross-sectional view taken along line 4B-4B of Fig. 4A.

Fig. 5 is a schematic illustration showing the relative sizes and convergence angles of the feed tube lumen and dispersion gas conduits of the present invention.

Fig. 6 illustrates a feed tube lumen in combination with a dispersion gas conduit having an annular aperture which defines a conical flow path.

Fig. 7 is a perspective view of an alternative feed tube assembly constructed in accordance with the principles of the present invention.

Fig. 20A is a top view of the receptacle being placed onto a carrier of the apparatus of Fig. 13.

Fig. 21 is a cross-sectional side view of the apparatus of Fig. 13.

Fig. 22 is a side view of the apparatus of Fig. 13 having its outside cover removed.

Fig. 23 is a side view of a handle assembly along with other selected components of the apparatus of Fig. 13, with the handle assembly being shown in a closed configuration.

Fig. 24 is a more detailed view of selected components of the apparatus of Fig. 23 and shows a release valve in an open configuration.

Fig. 25 illustrates the handle assembly and other selected components of Fig. 23, with the handle assembly being extended to close the release valve and retract a piston according to the present invention.

Fig. 26 is a more detailed view of the release valve of Fig. 25 shown in the closed position.

Fig. 27 is a perspective view of the release valve of the apparatus of Fig. 13.

Fig. 28 is a cross-sectional view of the release valve of Fig. 27 showing the valve in an open configuration.

Fig. 29 is a cross-sectional view of the release valve of Fig. 27 with the valve being in a closed configuration.

DESCRIPTION OF THE SPECIFIC EMBODIMENT

Referring now to Fig. 1, a system 10 for dispersing a powder medicament from a plurality of receptacles 12 by insertion of a feed tube assembly 14 will be described. The receptacles may be in any form that holds and preserves the medicaments and which provides a puncturable access surface. As illustrated, receptacles 12 are in a continuous web comprising individual wells covered by a puncturable lid, typically a metal foil or other conventional laminate. Each receptacle will include a precise dosage of the powdered medicament to be delivered. The amount of powder in each

sequentially advanced past a fluidization location (defined by the inlet end 16 of feed tube assembly 14) within the cartridge 22, with the receptacle which is at the dispersion or fluidization location being brought proximate the inlet end 16 of the feed tube to permit emptying of its powdered contents, as described in more detail hereinafter. Both reciprocation of the cartridge 22, and advance of the receptacles 12 within the cartridge, may be accomplished manually by the user. Alternatively, a mechanism may be provided within the base enclosure 11 for simultaneously reciprocating the cartridge 22 and advancing the strip of receptacles 12, either as part of a manual advance mechanism or as part of a battery-powered mechanism.

In the embodiment of Fig. 1, penetrations will be formed in the lid of the strip of receptacles 12 by a piercing mechanism 24. As illustrated, the piercing mechanism 24 will be fixedly mounted within the base enclosure 11 and will include a plurality of sharpened penetrating elements 26 disposed to contact and penetrate the puncturable lid 92 (Fig. 3) of the receptacles 12 when the cartridge 22 is reciprocated, as illustrated in broken line in Fig. 1. The piercing mechanism 24 will be located to contact a receptacle 12 which is located one station prior to the feed tube assembly 14. Thus, each receptacle 12 will be pierced immediately prior to being advanced to the fluidization location.

It will be appreciated that a wide variety of mechanisms can be provided for piercing holes within the lid of each receptacle and for bringing the receptacle into proximity with the feed tube assembly 14. For example, the cartridge 22 could be held stationary within the base enclosure 11 while each of the feed tube assembly 14 and piercing mechanism 24 could be reciprocated, either together or separately. Alternatively, the inlet end 16 of the feed tube assembly 14 could be configured to be self-penetrating (see Figs. 10 and 11A and 11B below). In the latter case, the desired pattern of penetrations would be formed in the puncturable lid of the receptacle 12 at the same time that the

Gas source 20 may be in the form of a manual pump, an electric pump, a high pressure gas cylinder, or the like. The construction of manual pumps in hand-held powder dispersion devices is described in the patent and technical literature. See e.g., WO90/07351. The construction of electric gas pumps, gas cylinder supplies, and two-fluid systems is also well within the skill in the art.

The gas dispersion system 10 further includes a plume capture chamber 30 which is disposed over the outlet end 18 of feed tube assembly 14 in order to capture powder released from the tube. The plume chamber 30 will include a mouth piece 32 at its distal end and will have an internal volume sufficient to capture substantially all of the powder dispersion which is delivered from the feed tube assembly 14. Usually, the volume will be in the range from 50 ml to 1000 ml, preferably from 100 ml to 750 ml. The chamber 30 will also include an ambient air inlet (not shown), optionally a tangential inlet as described in co-pending Application Serial No. 07/910,048, the full disclosure of which is incorporated herein by reference. Alternatively, the air inlet can be axial or spiral, as described in connection with Figs. 7-9, below.

In operation, the powder dispersion will be introduced into the plume capture chamber 30, as illustrated by arrows 34. Air will be displaced through the mouthpiece 32, and optionally back through an annular lumen in the feed tube assembly 14, as indicated by arrows 36 and as will be described in more detail in connection with Fig. 2. Such recycling of air from the plume capture chamber 30 as the fluidization gas enters greatly reduces the total volume of new gas being introduced to the system. The only new gas introduced (prior to patient inhalation) will be from the gas source 20. After the entire contents of a receptacle 12 has been dispersed and captured within the plume chamber 30, the patient will inhale the entire aerosolized dose through the mouthpiece 32 chased by ambient air through the chamber to extract all aerosolized medicament from the chamber. Optionally, an orifice plate or other flow limiting element

area (A_2), although such a construction would be less preferred.

Referring to Fig. 4A, a mixing volume 60 having a uniform (non-expanding) cross-sectional area (A_3) and a length (L_2) is located immediately at the outlet end 18 of the feed tube 40. The cross-sectional area (A_3) is shown to be slightly larger than feed tube throat area(A_2) outlet, but this is not necessary. The exemplary area(A_3) is typically in the range from 0.6 mm^2 to 11 mm^2. The length (L_2) is 1-5 times the diameter of the mixing volume 60 (for circular cross-sections), typically being in the range from 0.5 mm to 2 mm. In the illustrated embodiment, a pair of gas conduits 54 (Fig. 4B) are shown, as illustrated in Fig. 4B. It would also be possible to utilize only a single inlet jet or to provide three, four or more separate inlets, with four inlets 54' being as illustrated in Fig. 4C. Other configurations will also be usable including a continuous annular aperture, as described in connection with Fig. 6, or combinations of perpendicular jets (to break-up agglomerates) and axially directed jets (to induce fluidization gas flow).

Referring now to Fig. 5, high pressure gas conduits 72 are arranged around the throat of a feed tube lumen 70 at angles α_1, and α_2, which will usually but not necessarily be equal. The angles α are important to achieving both adequate mass transfer of powder from the receptacle and adequate "agglomerate break up" as the powder enters the mixing volume immediately downstream from the outlet orifices of the conduits 72. The angles α will be in the range from 12.5° to 65°, preferably being from 25° to 40°.

It will be appreciated that the high pressure gas lumens 72, as illustrated in Fig. 5, may be formed as a single conical plenum 80 terminating in an annular aperture 82, as illustrated in Fig. 6. The angle of convergence α will generally be within the range set forth above for α above, and the total area of the annular lumen 82 will generally be within the total area A_2 for the high pressure gas lumens also set forth above. Typically, the conical plenum 80 will have a width w in the range from about 0.005 mm to 0.1 mm.

assembly 14 and can be used in place thereof in the system of Fig. 1. The feed tube 100, however, is particularly suitable for fabrication from molded plastic parts, or from a combination of molded plastic and fabricated metal parts.

Feed tube assembly 100 comprises a casing 102, a gas flow-directing cone 104, a feed tube element 106, an end piece 108, a flexible valve element 110, and an end gasket 112. The feed tube element 106 is received in an open cavity 114 disposed in a lower end of the flow-directing cone 104. The flow passages within feed tube 106 will generally be the same as that described previously for feed tube assembly 14, and feed tube assembly 100 further includes a mixing volume 116 located immediately above the open cavity 114 and an expansion region 118 located above the mixing volume. The dimensions of the mixing volume 116 and expansion region 118 will generally be the same as those described previously in connection with the feed tube assembly 14.

As best seen in Fig. 8, the flow directing cone 104 may include a plurality of air flow channels 120 formed over its exterior surface. Usually, there will be from 1 to 10 channels, having a total cross-sectional area from 5 mm^2 to 150 mm^2, preferably from 40 mm^2 to 100 mm^2. The air flow channels 120 are shown in a generally spiral pattern in Fig. 8. The spiral pattern may be preferred since it will impart a vortical flow to replacement air entering the associated plume chamber as the patient inhales. The airflow channels 120, however, could also have a generally straight configuration which would impart a conically expanding, but not spiral, flow pattern to the replacement air. It would also be possible to employ air flow channels which are straight and parallel to each other to impart a general axial replacement airflow pattern into the plume chamber. It will also be possible to employ a single annular opening by using pins of other non-dividing elements for supporting the flow-direction cone, where the cone may have a continuous surface without discrete channels.

The airflow channels 120 are enclosed at their outward extremities by the inner surface 122 (Fig. 9) of the

beyond the attachment point of the blade structure 144 to the inside wall of the host tube.

A plurality of similar penetrating structures 150 are provided for both piercing the receptacle lid and simultaneously providing fluidization air inlet paths. The penetrating structures 150 may be provided in a carrier plate 152 or similar supporting structure. The penetrating structures 150 will have a similar conical blade structure to that described previously for the feed tube penetrating structure 140. Thus, the structure of Fig. 10 can provide for both the feed tube penetration and the peripherally arranged fluidization air penetrations in the penetrable lid of a medicament receptacle in a single motion where the lid is drawn against the gasket 112 of the feed tube assembly 100.

Fig. 11B illustrates an alternative penetrating structure 151 formed by machining the end of a tube along two converging planes. The resulting pointed elements are then pressed together to form the structure having openings 153. The penetrating element 151 is advantageous since it peels back the lid as it is penetrated, leaving the openings 153 clear to receive powder. The penetrating structure 151 could be fabricated from molded plastic as well as machined metal.

Referring now to Figs. 12A-12C, use of the feed tube assembly 100 of Figs. 7-9 will be described in more detail. Initially, a medicament receptacle R having preformed feed tube and fluidization air penetrations 200 and 202 is engaged against the gasket 112, as illustrated in Fig. 12A. Gasket 112 provides a seal against penetrable lid 204 of the receptacle R. The inlet end of feed tube 106 is shown to penetrate the lid 104, but it will be appreciated that such penetration is not essential since a seal will be provided by the gasket 112. Penetration may be desirable, however, since the lid flaps which surround the penetration 200 will be held open.

After the receptacle R is in place, a burst of high pressure air is introduced into the open cavity 114, as shown in Fig. 12B. The high pressure air flows past outlet end of the feed tube 106, inducing a flow of fluidization air through

The capture chamber 304 is sized to be slidably received over the housing 302 so that the capture chamber 304 may be removed from the housing 302 for cleaning and also so that chamber 304 can be translated between a deployed position (see Fig. 20) and a retracted position (see Fig. 14). In the deployed position, the capture chamber 304 forms an enclosure for receiving aerosolized medicament introduced by the transjector assembly 306 so that it may be inhaled by a patient. Following inhalation, the capture chamber 304 can be slid over the housing 302 to the retracted position for storing. To hold the capture chamber 304 in the retracted and the deployed positions, two pairs of detent pins 308 and 310 are provided. The detent pins 308, 310 are received into slots 312 and 314 in the housing 302. Springs 316 and 318 are preferably provided to outwardly bias the detent pins 308, 310. The capture chamber 304 includes a chamber body 320 having a bottom portion 322 and a top portion 324. Included in the bottom portion 322 are a pair of grooves (not shown) for engaging the detent pins 308, 310. The detent pins 308 are received in the grooves when the capture chamber 304 is in the deployed position, and the detent pins 310 are received into the grooves when the capture chamber 304 is in the retracted position. The detent pins 308 and 310 each include a V-shaped portion 326 and 328 for engaging the grooves in the bottom portion 322 of the capture chamber 304. The particular angle and orientation of the V-shaped portions 326 and 328 can be varied to increase or decrease the amount of force required to deploy or retract the capture chamber 304. The mating grooves on the chamber 204 may also be provided with different angles to assist in achieving this effect. Usually, the detent pins 310 will be configured so that it is easier to translate the chamber 304 downward toward the bottom of the housing 302 than to translate the chamber 304 upward toward the top of the housing 302. In this manner, the chamber 304 may be placed in the retracted or storage position with a relatively small force, while a relatively greater force will be required to retrieve the chamber 304 from the storage position. In this way, the chamber 304 will be configured to

herein incorporated by reference, to limit the amount of electric charge built up on the walls of the chamber body 320 during use.

Referring to Fig. 14, the capture chamber 304 is shown in the retracted position and will be used to describe operation of the inhalation port 330 in greater detail. The capture chamber 304 includes a cover 344 that may be closed over the inhalation port 330. The cover 344 is employed to prevent external dust or particulate from entering into the interior of the capture chamber 304 during storage and also to hold the aerosolized medicament introduced by the transjector assembly 306 within the chamber 304 until ready for inhalation. Optionally, the cover 344 may include seal 346 which is received over the inhalation port 330 when the cover 344 is closed. When introducing the aerosolized medicament, the pressure within the capture chamber 304 is increased. The seal 346 serves as a bleed valve to allow some of the pressurized gas within the chamber 304 to spontaneously escape. Reducing the chamber pressure in this manner is advantageous in preventing a "puff" of medicament from escaping when the cover 344 is lifted for inhalation.

The capture chamber 304 will preferably define an enclosed volume of about 50 ml to 750 ml, and more preferably at about 100 ml to 250 ml. When the aerosolized medicament is introduced into the chamber 304, the pressure inside will increase over ambient in proportion to the amount of net gas exhausted into the chamber and the volume of the chamber as dictated by Boyles' law where $P_1V_1 = P_2V_2$, T = constant at equilibrium. For example, 8 ml of gas introduced into a 210 ml chamber will amount to a pressure rise of about 0.6 psi. Thus, it is desirable for the seal 346 to allow approximately 8 ml of gas to escape to drop the pressure by 0.6 psi. The seal 346 is preferably constructed of silicone, urethane or similar flexible elastomers, although a similar functioning valve could be achieved with a spring loaded rigid valve element such as a thin mylar or metal petal or plate.

Referring to Fig. 15, placement of the transjector assembly 306 into the housing 302 will be described in greater

structures 372 may optionally be provided with a plurality of points rather than a single point to facilitate penetration into the receptacle lid.

As best shown in Figs. 18 and 19, the receptacle 342 includes a receptacle body 374 having a penetrable lid 376 covering an enclosure 378 and a tab 380. Within the tab 380 is a hole 382 for aligning the receptacle 342 with the transjector assembly 306 as described in greater detail hereinafter.

To penetrate the lid 376, the receptacle 342 is lifted (or the transjector 306 is lowered) until the penetrating element 370 and the penetrating structures 372 pierce the lid 376 as shown in Fig. 19. The penetrating structures 372 are angled relative to the penetrating element 370 and operate similar to can openers to peel back a portion of the lid 376 and form the air inlet paths. Once the receptacle 342 is in place, a burst of high pressure air is introduced into an open cavity 384 which flows past the outlet end of the feed tube 362 to draw the powdered medicament within the receptacle 342 through the transjector assembly 306 in a manner similar to the feed tube assembly 100 described in Figs. 12-12C. When the penetrating element 370 and the penetrating structures 372 pierce the lid 376, the end gasket 368 contacts the receptacle body 374 and forms a seal against the receptacle 342.

Referring to Figs. 20 and 20A, placement of the receptacle 342 into the aperture 340 will be described in greater detail. The receptacle 342 is delivered into the aperture 340 by grasping the tab 380 and inserting the receptacle body 374 into the aperture 340 until stop shoulders 375 on the receptacle body 374 engages guide pins 377 (see also Fig. 21) on which a carrier 442 (see also Fig. 22) rides and prevents further translation. At this point, the hole 382 is generally aligned with a pin 386. The receptacle 342 is then lifted within the aperture 340 until the hole 382 is received over the pin 386 which guides and aligned the receptacle 342 until engaging the end gasket 368 (see Fig. 19). At all times, the tab 380 remains outside the

The release valve assembly 400 is in turn in communication with the transjector assembly 306 so that pressurized gas may be supplied to the open cavity 384 as previously described in Fig. 19. A seal 402 is provided between the valve assembly 400 and the transjector assembly 306 to prevent high pressure air supplied from the valve assembly 400 from escaping between the interface between the valve assembly 400 and the transjector assembly 306. The seal 402 is preferably constructed of urethane, silicone, or a similar elastomer, and is angled relative to a longitudinal axis of the transjector assembly 306. In this way, the transjector assembly 306 may easily be inserted and removed to and from the housing 302 while at the same time allowing for a sufficient interface seal.

The valve assembly 400 includes a valve stem 404 and a valve poppet 406 for selectively preventing air from flowing through the assembly 400 and will be described in greater detail hereinafter with reference to Figs. 27-29. In Figs. 21-24, the valve assembly 400 is shown in the open position, with the poppet 406 being unseated. In such a configuration, gas within the cylinder 390 will not be significantly compressed upon translation of the piston 388 since air within the cylinder 390 will escape through the outlet tube 398. When the valve assembly 400 is closed, air is prevented from escaping from the outlet tube 398 so that only a "full stroke" of air within the cylinder 390 may be compressed. In a particularly preferable aspect of the invention, the apparatus 300 is configured to close the valve assembly 400 as the piston 388 reaches the extended position so that air within the cylinder 390 may be compressed when the handle 338 is translated back toward the housing 302. To close the valve assembly 400 in this manner, the handle assembly 336 includes a linkage 408 (see Fig. 22) having rack 410 securely attached thereto. The rack 410 includes an elongate slot 412 for receiving a valve reset link 414 (see Figs. 21 and 24). As best shown in Figs. 21 and 24, the reset link 414 is pivotally attached to a roller cam 416. In turn,

handle 338 is prevented which would prematurely deliver air into the transjector assembly 306. Such premature delivery is undesirable if the user has already loaded and punctured the receptacle. Alternatively, an interlock may be provided to prevent piercing of the receptacle 342 by the transjector assembly 306 until the valve assembly 400 is closed.

Referring to Figs. 22 and 25, translation of the handle 338 relative to the housing 302 will be described in greater detail. The handle assembly 336 further includes a linkage 430 that is pivotally connected to the housing 302 by pin 432. Connecting the handle 338 to linkage 392 and linkage 408 is a linkage 434. Together, linkages 392, 408, 430 and 434 provide a four-bar linkage system which allow the handle 338 to be moved radially outward from the housing 302 with the handle 338 being maintained generally parallel to the housing 302. Further, when the valve assembly 400 is closed and the handle 338 is translated back toward the housing 302, a substantially uniform force is required over the handle's range of motion. In this way, as the user forces the handle 338 back toward housing 302 to compress the air in the cylinder 390, the user feels a generally equal resistive force during the entire compression step. Moreover, the maximum distance that the handle 338 is translated away from the housing 302 is reduced, thereby making it easier for smaller hand sizes to operate.

As best shown in Figs. 22 and 23, the apparatus 300 further includes a carriage assembly 436 for translating the receptacle 342 within the aperture 340 so that the penetrating element 370 and the penetrating structures 372 may pierce the lid 376 of the receptacle 342. The carriage assembly 436 includes a thumb toggle 438 that is pivotally connected to the frame of the housing 302 by a pin 440. The receptacle 342 is held within a carrier 442 which in turn is connected to the thumb toggle 438 by a linkage 444. Operation of the carriage assembly 436 is as follows. Initially, the receptacle 342 is inserted into the aperture 340 as previously described with the receptacle 342 resting on the carrier 442. The thumb toggle 438 is then depressed to pivot the toggle 438 about

about 120 psi of pressure, and more preferably at about 80 psi.

To open the valve assembly 400, the release button 418 is depressed to move the cam 416 from over center and to allow the poppet 406 to be moved away from the seat 452. To force the poppet 406 away from the seat 452, a spring 457 is provided. The spring 457 will preferably be selected to provide a force sufficient to overcome the force on the opposite side of the poppet that is produced by the compressed air within the chamber 454. Hence, when the release button 418 is depressed, the spring 457 will overcome the force produced by the compressed air within the chamber 454 and will promptly force the poppet 406 away from the seat 452 and allow the valve to open. The valve will rapidly open to allow the compressed air in the cylinder 390 and tube 398 to almost instantaneously rush out the central chamber 454 through the outlet port 450 where it is delivered to the transjector assembly 306 as previously described. In this manner, the valve assembly 400 operates in a "snap" acting manner to provide a precise amount of gas to the transjector assembly 306 in a rapid, abrupt and irreversible manner so that the powder may be sufficiently aerosolized in a repeatable and a predictable manner.

Optionally, the housing 302 may further include an electronic memory chip along with a speaker for providing audible instructions to a user regarding operation of the apparatus 300. The chip will preferably be an EPROM, PROM, or PAL chip having stored electronic information regarding operation of the apparatus 300 and will be configured to be actuated upon deployment of the capture chamber 304. In this way, as a user prepares for a treatment, audible instructions will be given. Preferable instructions include deployment of the chamber 304, charging of the apparatus with the handle assembly 336, breathing instructions, and the like, as well as other pertinent information as determined by the manufacturer.

Although the foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity of understanding, it will be obvious that

WHAT IS CLAIMED IS:

1. A method for aerosolizing a powder contained in a receptacle having an access surface, said method comprising:

coupling a powder inlet end of a feed tube with a penetration in the access surface; and

flowing a high pressure gas stream past a portion of the feed tube, so that predetermined amount of powder in the receptacle is fluidized, drawn axially through the tube, and dispersed in the high velocity air stream to form an aerosol.

2. A method as in claim 1, further comprising forming the penetration in the access surface prior to or during insertion of the feed tube, wherein the high pressure air stream is flowed past the feed tube at an angle in the range from 12.5° to 65° relative to the axial direction, and wherein the predetermined amount is at least 70% by weight of the amount of powdered medicament initially present in the receptacle.

3. A method as in claim 1, further comprising forming at least two spaced-apart penetrations in the access surface, wherein the other penetration permits fluidization air to sweep the receptacle as the powder is drawn through the feed tube, further comprising advancing a plurality of powder-containing receptacles past the feed tube, whereby powder may be drawn sequentially and dispersed from each receptacle, wherein a fixed volume of high pressure gas in the range from 2 ml to 25 ml (STP) is flowed past the outlet end, resulting in a discrete volume of aerosolized powder, further comprising capturing substantially the entire volume of aerosolized powder in a plume capture chamber, wherein the powder is available for subsequent inhalation by a patient, and wherein at least a portion of gas in the chamber is directed back to the receptacle to provide fluidization gas as the powder is withdrawn through the feed tube.

chamber to the receptacle, whereby said directed air will enter the receptacle to provide fluidization air as powder is drawn therefrom.

7. Apparatus as in claim 4, further comprising a plume capture chamber disposed on the base to capture powder dispersed in said high velocity air stream, said chamber having a mouth piece at an end remote from the base, and wherein the means for flowing comprises a pump or other pressurized gas source in the base enclosure for abruptly releasing a pressurized volume of air to form the high velocity air stream.

8. Apparatus for aerosolizing a powder, said apparatus comprising:

a feed tube having an inlet end, an outlet end, and a lumen defining an axial flow path therebetween; and

means for flowing at least one high pressure gas stream past said outlet end in a direction which converges with the axial flow path at an angle in the range from 12.5° to 65°.

9. Apparatus as in claim 8, wherein the flowing means includes at least one gas conduit which converge with the flow path, wherein the flowing means provides a total lumen area (A_1) in the range from 0.05 mm^2 to 0.3 mm^2 and the feed tube has a lumen area (A_2) in the range from 0.5 mm^2 to 10 mm^2, further comprising an diffuser tube extending from the outlet end of the feed tube and having a lumen coaxially aligned with the feed tube lumen, wherein the diameter of the diffuser tube lumen increases in a direction away from the outlet end of the feed tube, and wherein the diffuser tube lumen diverges at a half angle of 2° to 10° over a length in the range from 0.5 cm to 5 cm.

14. An improved apparatus for aerosolizing a powdered medicament, the apparatus being of the type having a housing and a source of pressurized gas for aerosolizing the powder, wherein the improvement comprises:

a pressurization cylinder;

a piston slidable within the cylinder;

a release valve in communication with the cylinder; and

a handle assembly having a handle operably attached to the piston and a means for closing the valve, wherein translation of the handle closes the valve and axially translates the piston within the cylinder to produce the pressurized gas.

15. An improved apparatus as in claim 14, wherein the release valve comprises a valve stem connected to a valve poppet, wherein the means for closing the valve comprises a roller cam adjacent the valve stem for translating the valve stem to close the valve as the handle is translated radially outward from the housing, wherein the handle assembly further comprises a toggle link which moves over-center to hold the roller cam against the valve stem and keep the valve closed, wherein the handle assembly further includes a linkage between the handle and the piston, wherein the linkage reciprocally translates the piston between a retracted position and a charged position within the cylinder as the handle is translated radially outward and radially inward relative to the housing, further comprising an interlocking means for preventing inward radial translation of the handle until the toggle link has moved over-center, and wherein the interlocking means comprises a ratchet and a pawl.

19. An apparatus for aerosolizing a powder held in a receptacle having a puncturable access surface, the apparatus comprising:

a housing;

a source of pressurized gas;

a capture chamber attached to the housing; and

a transjector assembly held within the housing, said transjector assembly having a means for piercing the access surface of the receptacle and for receiving pressurized gas to draw powder from the receptacle and into the capture chamber.

20. An apparatus as in claim 19, wherein the transjector assembly receives gas directly from the gas source and delivers powder directly to the capture chamber without powder passing through other portions of the apparatus, further comprising an interface seal between the transjector assembly and the housing, whereby pressurized gas may be passed from the housing to the transjector assembly without substantial loss of the gas, and wherein the interface seal is angled relative to a central axis of the transjector assembly.

21. An apparatus as in claim 19, further comprising a receptacle seal for forming a seal between the transjector and the receptacle, wherein the transjector assembly is keyed to be repeatedly received into the housing in a unique orientation, wherein the capture chamber is axially slidable over the housing, whereby the capture chamber may be placed in a collapsed position substantially covering the housing or an extended position forming an enclosure for receiving aerosolized powder, and further comprising at least one detent pin in the housing and at least one notch in the capture chamber, with the detent pin being received into the notch when the capture chamber is in the extended position.

22. An apparatus as in claim 19, wherein the capture chamber further includes a mouthpiece, further comprising a cap removably held over the mouthpiece, and further comprising a seal between the cap and the mouthpiece.

handle being generally parallel to the housing, and further comprising supplying a generally constant force when translating the handle toward the housing when pressurizing the gas.

27. An improved method as in claim 25, further comprising introducing the powder that is suspended in the released gas into a capture chamber while simultaneously bleeding off a preselected amount of gas from the capture chamber, further comprising providing a transjector assembly for receiving the pressurized gas and aerosolizing the powder, and periodically removing the transjector assembly from the housing for cleaning.

28. An improved method as in claim 25, further comprising providing a receptacle having a puncturable lid for holding the medicament and translating the receptacle toward the transjector assembly until the transjector assembly penetrates the lid, further comprising guiding the receptacle toward the transjector so that the transjector penetrates the lid at a known and a predictable position, and further comprising holding the receptacle with the transjector assembly penetrating the lid until after the valve is released.

29. A method for aerosolizing a powdered medicament, said method comprising:

providing receptacles having a receptacle body and a tab extending from the receptacle body, wherein the powdered medicament is held within the receptacle bodies;

inserting one receptacle into a housing having an aperture, wherein the receptacle body is received within the aperture and at least a portion of the tab remains outside the housing;

piercing the receptacle body and extracting the powdered medicament in a gas stream that can be inhaled;

pulling on the tab to remove the receptacle from the housing.